REMARKS

This application has been amended in a manner that is believed to place it in condition for allowance at the time of the next Official Action.

Claims 7, 10, 11, 13, 19, and 34-35 have been amended. New claims 64 and 65 have been added. The specification has been amended so that the phrase "as claimed in one of claims 7 to 11" has been deleted. As the claims may change throughout the prosecution of an application, the deletion of this phrase is deemed proper and reflects preferred U.S. patent practice.

Independent claim 7 has been amended to recite a peptide compound comprising a sequence of at least 8 consecutive amino acids. The sequence has at least one modification or mutation and exhibits at least 80% homology with an amino acid sequence comprised between amino acids 286 and 294 of natural hsp70. The peptide compound is capable of inducing a specific anti-tumoral T-cell immune response. Support for amended claim 7 may be found at page 4, line 27, to page 5, line 10, and page 7, lines 1-11.

Claims 8-10, 11, 13, 19, and 34-35 have been amended to more particularly point out and distinctly claim the subject matter of the present invention. It is believed

that no new matter has been introduced into the present application.

In the outstanding Official Action, claims 7-10, 13, 14, 19-21, 30, 31 and 34-35 were rejected under 35 USC §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. This rejection is respectfully traversed.

Claims 7 and 35 were rejected for allegedly being indefinite for containing the phrase "T-response". As thoughtfully suggested by the Examiner, claims 7 and 35 have been amended to recite the phrase "T-cell immune response". Thus, it is respectfully submitted that claims 7 and 35 are definite to one of ordinary skill in the art.

Claim 19 was rejected for reciting the phrase "mixture of peptides". Claim 19 has been amended to recite a pharmaceutical composition comprising a peptide compound according to claim 7 and a pharmaceutically acceptable vehicle. Thus, it is believed to be apparent that claim 19 is definite to one of ordinary skill in the art.

Claims 34 and 35 were rejected for allegedly being indefinite for reciting the terms "ex situ" and "in situ". Applicants respectfully submit that one of ordinary skill in

the art would find the terms "ex situ" and "in situ" definite.

Claims 34 and 35 are directed to a method of immunizing a patient. Applicants believe that in light of the present specification, one of ordinary skill in the art would understand that the method of administering the claimed peptide compound can be accomplished by injecting the peptide compound in a tumor or at an area away from the tumor. Nevertheless, in the interest of advancing prosecution, claims 34 and 35 have been amended so that these terms are no longer recited in the claims.

In claim 34, the term "ex situ" has been deleted and the phrase "at a distance from a tumor(s)" has been inserted. In claim 35, the term "in situ" has been deleted and the phrase "by direct injection in a tumor(s) or at an immediately vicinity of a tumor(s)" has been inserted. Thus, it is respectfully submitted that claims 34 and 35 are definite to one of ordinary skill in the art.

In the outstanding Official Action, claims 11, 13-14 and 21 were rejected under 35 USC §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had

possession of the claimed invention. This rejection is respectfully traversed.

Applicants believe that the present disclosure clearly satisfies the written description requirement of 35 USC §112, first paragraph. As the Examiner is aware, an applicant's disclosure need only reasonably convey to the skilled artisan that as the filing date of the application relied upon, the applicant had possession of the specific subject matter claimed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 19 USPQ2d, 1111 (Fed. Cir. 1991).

The claimed invention is directed to a peptide compound comprising a sequence of at least 8 consecutive amino acids of a natural hsp70 sequence. The sequence has at least one mutation or modification and exhibits at least 80% homology with the amino acids sequence comprised between amino acids 286 and 294 of natural hsp70. The peptide is capable of inducing a specific anti-tumoral T-cell immune response.

Thus, the claims no longer recite general references to "peptide fragments". Moreover, the claimed invention has been amended to provide scope and clarity to the term "elements". Claim 11 has been amended so that the "element" of the claimed invention may be selected from a Markush group. The Examiner's attention is respectfully

directed to page 8 of the present specification, wherein the compounds from which the "element" may be selected from are clearly recited in the present disclosure.

The Examiner's attention is also respectfully directed to page 7, lines 1-18 in the present specification where it is stated that the claimed peptide compound may be characterized by a sequence of at least 8 consecutive amino acids of hsp70. The compound has at least one mutation or one modification with respect to the natural hsp70 sequence. The specification also states that the peptide compound may have at least 80% homology with the amino acids between positions 286 and 294 of hsp70.

Moreover, the present specification teaches that the amino acid position 293 may be isoleucine, leucine, valine, alanine, glycine or phenylalanine. In fact, the present specification identifies SEQ ID No. 1 and SEQ ID No. 2 as preferred peptide compounds of the present invention. Thus, it is respectfully submitted that the present specification clearly discloses to one of ordinary skill in the art that applicants were in possession of the claimed invention at the time the application was filed.

Applicants agree that a disclosure which represents just a wish, or arguably a plan, for obtaining a novel nucleic acid, or even a peptide, is not adequate

because a conception of such a compound requires a precise definition, such as by structure, formula, chemical name, or physical properties, and therefore a description of such a compound also requires some degree of specificity. *Fiers v. Sugano*, 984 F.2d 1164, 25 USPQ 2d 1601 (Fed. Cir. 1993); *Amgen Inc. v. Chugai Pharm. Co. Ltd.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991); and *Regents of Univ. of Calif. V. Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

However, applicants respectfully submit that the present specification clearly describes more than just a wish or mere plan for a peptide compound.

The present specification discloses the structure and physical properties of the amino acids involved in the present invention. The peptide compound is described in structural terms and properties exhibited by the peptide compound beginning on page 7. Moreover, the present specification discloses a ~~variety~~ of structures that exemplify the claimed invention. Thus, it is respectfully submitted that the present specification provides a precise definition as to the structure and physical properties of the claimed invention.

Thus, applicants respectfully submit that the present disclosure notifies one of ordinary skill in the art

that applicants were in possession of the claimed invention at the time the application was filed.

In the outstanding Official Action, claims 11, 34, and 35 were rejected under 35 USC §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one of skill in the art to which it pertains, or with which it is most clearly connected, to make and/or use the invention. This rejection is respectfully traversed.

Applicants respectfully submit that one of ordinary skill in the art would be enabled by the present disclosure to make and use the claimed invention. The present disclosure describes the claimed peptide compound in terms of structure and property. Moreover, the present specification clearly provides several examples for one of ordinary skill in the art to follow.

As the Examiner is aware, the test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, is it undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). In fact, a disclosure is enabling even if a considerable amount of experimentation is involved, if it is merely routine and not unduly extensive. Ex parte *Formal et al.*, 230 USPQ 546, (BPAI 1986). See also *Katrapat AG v.*

Advance Machine, 28 USPQ2d 1270 (ND Ill 1993). Applicants respectfully submit that it would not be an undue burden for one of ordinary skill in the art to practice the present invention commensurate in scope with the claims. The claimed peptide compound is not directed to an unlimited amount of sequences. One of ordinary skill in the art would be able to determine the sequences of the claimed invention.

Thus, when considering there is a limited amount of sequences involved, an endless or limited amount of experimentation would not be necessary. One of ordinary skill in the art would clearly be able to make and use the claimed peptide compounds. Although it is respectfully submitted that a considerable amount of experimentation is not needed, any experimentation that would have to be done certainly would be routine. One of ordinary skill in the art would clearly be able to practice the present invention when considering the limited number of sequences involved.

In the outstanding Official Action, claims 7-10, 13, 19, 21, 30, 34 and 35 were rejected under 35 USC §102(b) as allegedly being anticipated by Dragon et al.

Applicants believe that Dragon et al. fail to disclose or suggest the claimed invention. Dragon et al. relate to the preparation of vaccines based on protein homology of heat shock proteins from *T. cruzi*. Dragon et

al. provide the gene and derived amino acid sequence to T. cruzi hsp70 (Figure 1). Dragon et al. then utilize a DNA sequence as a probe to get hsps (or fragments or derivatives) from other organisms. The hsps have at least 50% homology with *T. cruzi* hsp and are capable of being used for immunizing a subject against said organism. Examples of organisms are given on page 3 and mostly comprise Mycoplasma or Mycobacteria. Hsp70 DNA sequences are aligned, and in particular human hsp70 (Figure 2.6).

However, Dragon et al. do not describe nor suggest the possible use of hsps to induce an anti-tumoral immunity, as in the present application. The Human hsp70 sequence is described, but its possible use in immunization protocols is not suggested. Moreover, Dragon et al. use hsp70 from a given organism as a product designed to immunize against a whole antigen. Dragon et al. use the entire hsp70 protein, or their equivalents, for immunization (page 32). Thus, Dragon et al. do not cite the possible use of hsp derived peptides for inducing a hsp70 specific immune response. In fact, Dragon et al. emphasize the importance of the epitope structure (page 9, lines 12-32). Thus, applicants believe that Dragon et al. do not disclose or suggest the claimed peptide compound. Therefore, the present invention is not anticipated by Dragon et al.

In the outstanding Official Action, claims 7-10, 13, 19-21, 30-31 and 34-35 were rejected under 35 USC §103(a) as allegedly being obvious in view of Dragon et al. and further in view of Prakken et al. and Costa et al. However, applicants believe that the Prakken et al. and Costa et al. publications fail to remedy the deficiencies of Dragon et al. As such, applicants respectfully traverse the rejection.

The COSTA et al. publication relates to the comparison of antibody responses to different forms of 18kDa heat-shock protein (18 Kda hsp) from *Mycobacterium leprae*. Mice were administered either unmodified 18 Kda-hsp, 18 Kda-hsp conjugated with BSA, or 18 Kda-hsp esterified with N-hydroxysuccinimide ester of palmitic acid, the protein being either free or linked to liposomes. Results show that the injection of an entire 18 kDa Mycobacterial protein stimulates the production of specific antibodies. However, the COSTA et al. publication does not disclose nor suggest the use of specific peptides derived from a hsp protein, nor the possibility of induction of a T cell response by using such immunogen.

As to PRAKKEN et al., the publication discloses that adjuvant arthritis (AA) is an auto-immune disease that can be induced by rats by immunization with mycobacterial

antigens or by passive transfer of a T cell clone recognizing a 180-188 amino acid sequence of hsp60. PRAKKEN et al. describe an arthritis suppressive mechanism, which can be triggered by the induction of tolerance towards the hsp60 180-188 epitope. Thus, the PRAKKEN et al. document describes a particular peptide having an amino acid sequence identical to an amino acid sequence from a mycobacterial Hsp60 protein.

In addition, applicants note that the hsp60 peptide is mixed with adjuvants such as Freund adjuvant or DDA, which are not suitable for human immunization. Applicants also note that Dragon et al. state that hsp proteins are comparable from one species to another provided they are homologous, therefore while hsp70 proteins may be compared with other hsp70 proteins applicants believe that one of ordinary skill in the art would not compare Hsp60 proteins with hsp70 proteins. Thus, applicants believe that the combination of Dragon et al. with Prakken et al. and Costa et al. fails to describe or suggest the claimed invention.

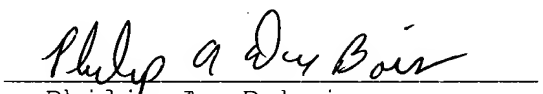
In view of the present amendment and the foregoing remarks, therefore, it is respectfully believed that this application is now in condition for allowance. Allowance

and passage to issue on that basis are accordingly respectfully requested.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

Respectfully submitted,

YOUNG & THOMPSON

By 

Philip A. Dubois
Agent for Applicants
Registration No. 50,696
745 South 23rd Street
Arlington, VA 22202
Telephone: 521-2297

January 3, 2003

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

Page 12, the second full paragraph was amended as follows:

--The present invention also relates to the use of a peptide compound [as claimed in one of claims 7 to 11,] for manufacturing a medicinal product, in particular intended for treating cancer, particularly solid tumors, especially carcinomas, melanomas, neuroblastomas and neck and head cancers, preferably renal carcinomas. This medicinal product can be intended for immunization ex situ or in situ. The invention also relates to the use of said peptide compound for increasing, in culture medium, the tumor CTL population and/or inducing the secretion by said CTLs of cytotoxic factors, such as for example IL-2, IFN-γ or TNF, and/or for stimulating the immune defenses, in particular so as to increase the tumor CTL population and/or induce the secretion by said CTLs of cytotoxic factors, such as for example IL-2, IFN-γ or TNF.--

IN THE CLAIMS:

The claims were amended as follows:

--7. (THREE TIMES AMENDED) A peptide compound comprising a sequence of at least 8 consecutive amino acids of a natural hsp70 sequence, the sequence having at least one mutation or modification with respect to, and having at least 80% homology with, the amino acids sequence comprised between amino acids 286 and 294 of natural hsp70, said peptide being able to induce [the natural hsp70 sequence, and wherein the peptide compound brings about] a specific [T] T-cell immune response.--

--8. (twice amended) The peptide compound as claimed in claim 7, wherein the amino acid sequence is selected from the group consisting of: SLFEGIDIY (SEQ ID No 1), SLFEGIDIYT (SEQ ID No 2), SLFEGIDLY, SLFEGIDVY, SLFEGIDAY and SLFEGIDGY [having at least 80% homology with amino acids between positions 286 and 294 of the natural hsp70 sequence].

--9. (TWICE AMENDED) The peptide compound as claimed in claim [8] 7, wherein the amino acid sequence is selected from the group consisting of: SLFEGIDIY (SEQ ID No 1) and SLFEGIDIYT (SEQ ID No 2) [wherien the amino acid at position 293 is chosen from isoleucine, leucine, valine, alanine, glycine and phenylalanine].--

--10. (TWICE AMENDED) The peptide compound as claimed in claim 9, [comprising at least one] wherein the amino acid sequence [chosen from] is SEQ ID No. 1 [and SEQ ID No. 2].--

--11. (THREE TIMES AMENDED) The peptide compound as claimed in claim 7, further comprising at least one element [other than natural amino acids, wherein the element provides at least one of the following functions regarding the peptide compound: chemical protection, physical protection, promotion of absorption by the body, promotion of administration, and promotion of bioavailability] selected from the group consisting of:

- a protective chemical group reacting with the NH2 or COOH, or with both NH2 and COOH, provided that this modification does not significantly lower the immunogenicity of the peptide,

- a chemical group improving the effectiveness of a vaccine in vivo,

- lipids or fatty acids, covalently linked to the peptide fragments so as to form lipopeptides,

- a carrier protein possessing restriction sites and enabling intact peptide fragments to be conveyed to their sites of action in the body.--

--13. (THREE TIMES AMENDED) A vector for expressing the peptide compound as claimed in claim 7, comprising a DNA fragment encoding [a] for said peptide [fragment of hsp70] compound, wherein the DNA fragment is fused to a promoter that is strong and effective in eukaryotic or in prokaryotic cells or in both eukaryotic and prokaryotic cells.—

--19. (TWICE AMENDED) A pharmaceutical composition comprising a peptide compound[, or a mixture of peptide compounds, as claimed in] according to claim 7 and a pharmaceutically acceptable vehicle.--

--34. (TWICE AMENDED) A method for immunizing [ex situ] at a distance from a tumor(s), comprising administering to a patient a medicinal product comprising a peptide compound comprising a sequence of at least 8 consecutive amino acids of a natural hsp70 sequence the sequence having at least one mutation or modification with respect to the natural hsp70 sequence, and wherein the

peptide compound brings about a specific [T] T-cell immune response.--

--35. (TWICE AMENDED) A method for immunizing [in situ] by direct injection in a tumor(s) or at an immediate vicinity near a tumor(s), comprising administering to a patient a medicinal product comprising a sequence of at least 8 consecutive amino acids of a natural hsp70 sequence the sequence having at least one mutation or modification with respect to the natural hsp70 sequence, and wherein the peptide compound brings about a specific [T] T-cell immune response.—